Methenamine hippurate compared with antibiotic prophylaxis to prevent recurrent urinary tract infections in women: the ALTAR non-inferiority RCT

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Scientific summary

The ALTAR non-inferiority RCT

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Scientific summary

Background

Urinary tract infections (UTIs) are common in adult women and become recurrent in 30–40% of women following a single episode. Recurrent urinary tract infection (rUTI) is defined as two UTI episodes in 6 months or three episodes in 1 year. The current standard preventative treatment for rUTI is daily low-dose antibiotics, which are universally recommended by national/international guidelines and result in significant antibiotic use. Current strategies to combat rising antimicrobial resistance underline the importance of judicious antibiotic prescribing. Consequently, this trial was motivated by the need to determine whether or not the benefits of the non-antibiotic treatment methenamine hippurate (Hiprex®; Mylan NV, Canonsburg, PA, USA) that were observed in lower-quality trials could be confirmed in a large, well-regulated, pragmatic randomised controlled trial with the comparator of daily low-dose antibiotics. In addition, the trial was designed to assess the health economic performance of this non-antibiotic preventative treatment option in adult women with rUTI.

Objectives

The objective was to determine whether or not methenamine hippurate is an effective alternative to low-dose antibiotic prophylaxis for rUTI prevention. The null hypothesis tested was that non-antibiotic treatment (methenamine hippurate) is inferior to the standard treatment of daily low-dose prophylactic antibiotics for the prevention of rUTI in women and is less cost-effective to the NHS.

Primary objectives

- To determine whether methenamine hippurate was non-inferior to antibiotic prophylaxis in reducing symptomatic antibiotic-treated UTI incidence in women with rUTI over a 12-month treatment period.
- To determine the relative cost-effectiveness of methenamine hippurate and antibiotic prophylaxis in women with rUTI.

Secondary objectives

Clinical

- To determine the relative impact of the two trial treatments on the incidence of symptomatic antibiotic-treated UTI during the 6-month post-treatment period.
- To determine the total number of days spent taking urinary-specific antibiotics during the 12-month treatment period and 6-month follow-up period.
- To determine longitudinal change in antibiotic resistance patterns in *Escherichia coli* isolates from participants' urine and faecal reservoirs during the 12-month treatment period and 6-month follow-up period. (*E. coli* is the most commonly encountered urinary tract pathogen and perineal swabs provide assessment of the faecal flora.)
- To determine the number of microbiologically proven UTIs during the 12-month treatment and 6-month follow-up periods.
- To determine the incidence of asymptomatic bacteriuria during the study.
- To determine the incidence of hospitalisation due to UTI during the study.
- To measure participants' overall satisfaction with trial treatments.

Qualitative

- To determine patients' and clinicians' views regarding trial processes and participation.

Economic evaluation

- To determine the incremental cost per quality-adjusted life-year (QALY) gained at 18 months, based on responses to the EuroQol-5 Dimensions, five-level version (EQ-5D-5L).
- To determine incremental costs to the NHS and personal and social services measured at the end of the 18-month study period.
- To determine the relative efficiency of trial treatments over the patient's lifetime using an economic model.

Methods

Design

The design was a multicentre, pragmatic, open-label, randomised non-inferiority trial evaluating the clinical effectiveness and cost-effectiveness of two licensed treatments for rUTI prevention. Adult women with rUTI were randomised (1 : 1) to receive once-daily low-dose antibiotic prophylaxis (nitrofurantoin, trimethoprim or cefalexin) or twice-daily urinary antiseptic (methenamine hippurate) for 12 months. Participants were observed for 6 months after completion of the trial treatment. Crossover of participants between trial treatments was permitted.

Setting and participants

This was a UK multicentre trial recruiting participants from eight secondary care NHS organisations.

Inclusion criteria

- Women aged $\geq$ 18 years.
- Women with rUTI requiring prophylactic treatment.
- Women able to take at least one of nitrofurantoin, trimethoprim or cefalexin.
- Women able to take methenamine hippurate.
- Women able to give informed consent.
- Women able/willing to adhere to an 18-month trial protocol.

Exclusion criteria

- Women unable to take methenamine hippurate.
- Women unable to take any of the trial antibiotics.
- Women with correctable urinary tract abnormalities considered contributory to the occurrence of rUTI.
- The presence of symptomatic UTI (delayed trial entry permitted).
- Pregnancy or intended pregnancy in the next 12 months.
- Women who are breastfeeding.

Women who agreed to take part in the trial but were already taking methenamine hippurate or antibiotic prophylaxis were consented for participation and stopped preventative therapy for a 3-month washout period. Those declining the washout period were excluded.

Measurement of clinical outcomes

Primary

The primary outcome of symptomatic, antibiotic-treated UTI, self-reported by participants over the 12-month treatment period, was defined as the presence of at least one prespecified patient-reported or clinician-recorded UTI symptom together with the taking of a discrete treatment course of antibiotics. The end of a single episode of UTI was defined as occurring 14 days after the last dose of therapeutic antibiotics; if further antibiotics were prescribed or if symptoms restarted within 14 days, then this was counted towards the same episode. The primary outcome was determined by the collection of data from multiple sources, including participant UTI logs, participant-reported questionnaires and site-reported case report forms (CRFs). A prespecified hierarchy of evidence avoided double counting of episodes and a sample of cases were reviewed by an independent clinician. The incidence of the primary outcome was calculated as the total number of UTI episodes divided by the total observational period for each participant.

Secondary

The incidence of symptomatic, antibiotic-treated UTI self-reported by participants over the 6-month follow-up period was defined as for the primary clinical outcome.

The number of days for which participants were prescribed prophylactic or therapeutic antibiotics during the 12-month treatment period and 6-month follow-up period was calculated from CRFs and the interrogation of medical records.

Microbiologically proven UTIs were defined as per the primary outcome plus a concomitant positive urine culture from a urine sample sent to the central laboratory or reported by a local laboratory. A positive culture was defined as a single isolate at $\geq 10^4$ colony-forming unit (CFU)/ml or two bacterial isolates at $\geq 10^5$ CFU/ml.

Antimicrobial susceptibility testing to a panel of antibiotics was carried out on pathogens isolated in significant numbers from urine and on *E. coli* isolated from perineal swab samples submitted to the central laboratory during the trial period. Antimicrobial resistance in *E. coli* was defined as resistance to one or more antibiotics in the panel tested. Multidrug resistance (MDR) in *E. coli* was defined as resistance to at least one antimicrobial agent in at least three antibiotic categories.

Asymptomatic bacteriuria was defined as a significant positive urine culture in the absence of symptoms.

Hospitalisation due to UTI was defined as unplanned hospital admission for treatment of a UTI confirmed by health-care record and CRF review.

Participant satisfaction was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM) administered at 12 and 18 months.

Economic evaluation

An NHS perspective was used for economic analyses. Treatment costs were estimated from participant-reported health-care resource use over the trial period, trial medications and medication received to treat UTIs. The total treatment cost, presented as Great British pounds 2019, was estimated for each participant and summarised as total cost per participant for each study arm. Health-state utilities were derived from responses to the EQ-5D-5L administered at baseline and every 3 months post randomisation. QALYs were estimated using the area under the curve approach. Similarly to costs, QALYs were summarised as average total QALYs per participant. The mean costs and QALYs were compared and cost-effectiveness was expressed as incremental cost per QALY gained. A Markov model was designed to extrapolate trial findings beyond the 18-month follow-up period. Where appropriate, costs and QALYs were discounted at 3.5% per year.

Qualitative outcomes

Telephone interviews, using a topic guide, were conducted with both patients approached to participate in the trial and site staff involved in its conduct. Patients' views of trial processes, their experience of rUTI and antibiotic use were explored. Interviews were digitally recorded, transcribed verbatim, checked and anonymised. A thematic coding frame was developed and data were analysed thematically drawing on the constant comparative method. The overall headline results were made available to inform change in study procedures before the end of the first year of recruitment.

Statistical analysis

The trial was powered to assess non-inferiority in the absolute difference in UTI incidence over the 12-month treatment period, with the non-inferiority margin set as one UTI episode per year. We assumed that the average number of UTI episodes per year would be 0.975 in those randomised to antibiotic prophylaxis and 1.56 in those randomised to methenamine hippurate, equating to an estimated difference of 0.6 episodes per year (in favour of antibiotics). Assuming an actual difference of 0.6 UTI episodes per year (in favour of antibiotics) and a standard deviation of 0.9 UTI episodes per year, two groups of 87 patients were required to be 90% sure that the lower limit of a one-sided 95% confidence interval (CI) (or, equivalently, a 90% two-sided CI) was above the non-inferiority limit of 1. The attrition rate was estimated at 25%; therefore, the total sample size required was 232 (rounded to 240).

The main analysis of the primary outcome measure was performed in the modified intention-to-treat (mITT) population and contained all randomised participants with an observational period of at least 6 months. Pre-planned sensitivity analyses were performed in a strict intention-to-treat population and a per-protocol population, which included all participants achieving at least 90% compliance with any trial treatment. The absolute difference in incidence of symptomatic, antibiotic-treated UTI episodes between arms was estimated along with a 90% CI calculated using a resampling (bootstrap) procedure. The relative difference between treatment arms was also estimated using a mixed-effects negative binomial regression model with differences between centre included as a random effect and prior annual UTI frequency ($<$ four vs. $\geq$ four episodes per person-year) and menopausal status (premenopausal vs. menopausal/postmenopausal) included as fixed effects. A binary indicator of at least one episode of symptomatic antibiotic-treated UTI was analysed using a mixed-effects logistic regression model with adjustment, as above. Secondary outcomes of UTI incidence followed the same approach (with 95% CIs reported).

The proportions of participants demonstrating antibiotic resistance or MDR at baseline, during the 12-month treatment period and during the 6-month follow-up period were compared between treatment arms using a chi-squared or Fisher's exact test, as appropriate.

Treatment satisfaction, assessed by scale scores of the TSQM, were compared between arms using a two-sample *t*-test and an analysis of covariance model adjusted for prior UTI frequency and menopausal status.

All other outcome measures were summarised descriptively.

Results

A total of 240 out of 480 patients were randomised, indicating a high level of willingness to participate. The baseline characteristics of patients were similar between trial arms and representative of women presenting to secondary care with rUTI. Participants reported a mean number of seven UTIs in the year prior to randomisation. During the 12-month treatment period, the incidence rate of patient-reported symptomatic, antibiotic-treated UTIs decreased to 1.38 episodes per person-year (95% CI 1.05 to 1.72 episodes per person-year) in the methenamine hippurate arm and 0.89 episodes per person-year (95% CI 0.65 to 1.12 episodes per person-year) in the antibiotic arm, indicating substantial benefit from

both treatments. The absolute difference was only 0.49 episodes per person-year (90% CI 0.15 to 0.84 episodes per person-year), in favour of antibiotic prophylaxis. This difference did not exceed the predefined, strict, non-inferiority limit of one UTI, and the null hypothesis was rejected. Both mITT and per-protocol analyses confirmed non-inferiority. The UTI incidence rate in the 6 months following treatment completion was 1.72 episodes per year in the methenamine hippurate arm and 1.19 episodes per year in the antibiotic arm, indicating sustained benefit from both treatments. Only 52% of symptomatic UTI episodes with an associated urine sample during treatment were confirmed by positive urine culture, supporting the use of a primary outcome of clinically defined rather than microbiologically defined UTI. During treatment, a higher proportion of participants in the antibiotic arm (46/64, 72%) demonstrated antibiotic resistance in *E. coli* cultured from perineal swabs than did those in the methenamine hippurate arm (39/70, 56%), (p-value = 0.05). Urine culture results revealed that during treatment a higher proportion of participants and samples from those allocated to antibiotic prophylaxis demonstrated resistance to trimethoprim/co-trimoxazole and cephalosporins, respectively. These results suggest that, when compared with methenamine hippurate, the use of continuous low-dose antibiotic prophylaxis was a more significant factor in the induction of antimicrobial resistance in *E. coli* in this trial. Conversely, post treatment, a higher proportion of participants in the methenamine hippurate arm (9/45, 20%) demonstrated MDR in bacteria isolated from perineal swabs compared with those taken from participants in the antibiotic arm (2/39, 5%) (p-value = 0.06). Possible reasons for this include a more sustained effect on the faecal microbiome from antibiotic treatment and a greater frequency of UTI antibiotic use during follow-up in the methenamine hippurate arm. Total therapeutic antibiotic use during treatment was similar in both study arms, with a median total days of treatment of 16 days for those allocated to methenamine hippurate and 13 days for those allocated to antibiotic prophylaxis. Only four (1.7%) participants were hospitalised for UTI during the trial. All other secondary outcomes were similar in both study arms. Participant satisfaction at 12 months was high across both randomised arms, with a global satisfaction score of 77.3 in those randomised to methenamine hippurate and 80.6 in those randomised to antibiotic prophylaxis. Overall, the adverse event rate was low and comparable in both arms, as would be expected from a trial involving two licensed treatments for rUTI prevention. The attrition rate was close to that predicted during study design and reflective of the prolonged trial duration.

Over 18 months of follow-up, methenamine hippurate was, on average, less costly and more effective than antibiotic prophylaxis. The probability of methenamine hippurate being considered cost-effective if we were not willing to pay for an additional QALY was 51%, and increased as willingness to pay for an additional QALY increased, but never exceeded 70%. Over the longer term our conclusions changed in that antibiotic prophylaxis was, on average, less costly and more effective; however, there was a lot of uncertainty in this conclusion and the probability of antibiotics being considered cost-effective never exceeded 60%.

The qualitative embedded study highlighted key issues for participants regarding understanding the nature of the trial and the risks/benefits of participating. Early feedback was given to recruiting staff to improve processes. Recruiting staff reported few difficulties delivering the trial.

Limitations

This trial was unable to define whether treatment strategies were more effective in specific patient groups or whether one particular antibiotic was more beneficial. Progressive data loss during follow-up hampered economic evaluation.

Conclusion

This large randomised pragmatic trial in a routine NHS setting has clearly demonstrated that the non-antibiotic treatment methenamine hippurate is not inferior to current standard care (daily low-dose

antibiotics) in preventing rUTI in adult women. Results also suggest that antimicrobial resistance is proportionately higher in women taking antibiotic prophylaxis than in those taking methenamine hippurate. In the short term, methenamine hippurate appears to provide more benefits at a lower cost. These results support the routine use of methenamine hippurate as a first-line treatment for rUTI prevention.

Recommendations for research

Recommendations for further research include evaluation of other non-antibiotic preventative treatments for rUTI (particularly in other populations, e.g. those with complicated UTIs), longer-term studies of UTI prevention, more in-depth evaluation of antimicrobial resistance in response to low-dose antibiotic prophylaxis, determination of longer-term costs and benefits associated with the trial treatments and determination of potential costs associated with antibiotic resistance.

Trial registration

This trial is registered as ISRCTN70219762 and EudraCT 2015-003487-36.

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This report

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